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Neoadjuvant Therapy Offers Longer Survival than Upfront Surgery for Poorly Differentiated and Higher Stage Pancreatic Cancer

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Neoadjuvant Therapy Offers Longer Survival than Upfront Surgery for Poorly Differentiated and Higher Stage Pancreatic Cancer

Background: Neoadjuvant therapy for pancreatic cancer remains controversial. Our aim was to assess differences in survival, disease recurrence and histopathological tumour characteristics between patients treated with neoadjuvant therapy followed by subsequent surgery and patients undergoing upfront surgery.

Material and Methods: Out of 399 consecutive pancreatic ductal adenocarcinoma (PDAC) patients operated at Helsinki University Hospital in 2000 to 2015, 75 borderline resectable patients were treated with neoadjuvant therapy. Resectable propensity scored patients (n=150) underwent upfront surgery. Neoadjuvant therapy consisted of folfinirinox, single gemcitabine or combined with cisplatin, nab-paclitaxel or capecitabine with or without radiation. Survival was calculated with Kaplan-Meier and compared with the Breslow test. Survival was determined from the start of treatment, being the first day of treatment for patients treated with neoadjuvant therapy and the date of surgery for others.

Results: Between 2000 and 2015 median disease-specific survival (DSS) [34 (95% CI 29-39) vs. 26 (20-32) months, $p=0.016$] and disease-free survival (DFS) [22 (17-27) vs. 13 (9-17) months, $p=0.001$] were longer in patients treated with neoadjuvant therapy than in those undergoing upfront surgery. Survival differences were not significant in the 2000s but were, in turn, among patients treated in the 2010s with better survival for patients treated with neoadjuvant therapy [DSS 35 (25-44) vs. 26 (20-31) months, $p=0.008$ and DFS 25 (13-36) vs. 13 (6-21) months, $p=0.001$]. ~~Neoadjuvant therapy offered longer survival especially for patients~~ with poorly differentiated G3 tumours **HAD LONGER SURVIVAL** [DSS 30 (17-42) vs. 11 (8-15) months, $p=0.004$ and DFS 21 (11-31) vs. 7 (5-8) months, $p=0.001$] and higher stage IIB-III [DSS 34 (29-40) vs. 20 (14-26) months, $p=0.006$ and DFS 21 (12-29) vs. 10 (7-13) months, $p=0.001$].

Conclusions: Neoadjuvant therapy offers PDAC patients longer DSS and DFS than upfront surgery. Neoadjuvant therapy benefits especially borderline resectable patients with higher stage and poorly differentiated tumours.

Keywords: pancreatic cancer; neoadjuvant therapy; pancreatic surgery; tumour grade; survival

Introduction

Pancreatic cancer is one of the most fatal cancers with an extremely poor overall five-year survival rate ranging from 5% to 8% [1,2]. Effective treatment regimens are lacking and the fatality of the disease is due to aggressiveness, advanced or metastatic disease at diagnosis and high recurrence rate [3]. Pancreatic ductal adenocarcinoma (PDAC) represents >90% of all exocrine pancreatic malignancies and holds the worst survival [4]. Margin negative surgery combined with oncological treatment is the only curative-intent treatment option with substantially higher survival rate, however, only 15% to 20% of the patients appear operable [5,6]. Despite advantages in research over the past decades, five-year overall survival rate has not improved drastically [1,3,7], and it has been predicted that PDAC continues to cause even more cancer-related deaths by 2030 due to lack of effective treatments and early detection [8].

Recently, neoadjuvant therapy in the management of PDAC has been a target of avid research. In the best-case scenario neoadjuvant therapy can downstage locally advanced tumours and increase the likelihood of R0 resection in borderline resectable cases [9,10]. Neoadjuvant approach to borderline resectable patients can also identify patients who are unlikely to benefit from surgery due to advanced disease [9,11]. However, administration of neoadjuvant therapy for resectable PDAC is still controversial in terms of patient selection [12,13]. With high recurrence rates, it has been postulated that PDAC is most likely a systemic disease at diagnosis [14] and hence, should be treated with neoadjuvant therapy. Furthermore, research shows that patients more likely complete neoadjuvant than adjuvant therapy indicating that

systemic therapy before surgery increases the likelihood of multimodal treatment [15,16]. However, it has been debated if administration of neoadjuvant therapy may endanger the possibility of surgery in progressive disease [17]. It is unclear why some patients with PDAC survive longer than others with the same kind of treatment. Recently, PDAC research has focused on personalised medicine and thus, more reliable and adaptable patient-specific prognostic factors and treatment options are needed.

The aim of this study was to compare disease-specific (DSS) and disease-free survival (DFS) and histopathological tumour characteristics in patients treated with neoadjuvant therapy and patients undergoing upfront surgery. We also explored possible sub-populations who would preferably benefit from neoadjuvant therapy over upfront surgery.

Material and Methods

Patients

We conducted a search for PDAC patients from the Helsinki University Hospital database and found in total 399 consecutive PDAC patients operated between January 2000 and December 2015 of which 75 borderline resectable patients were treated with neoadjuvant therapy and subsequent surgery. Propensity scored patients with matched age, sex and time of surgery (n=150) underwent upfront surgery. Patient characteristics and survival data were collected from patient records and the Finnish Population Registry. Cause of death was obtained from Statistics Finland. The study was approved

by the Surgical Ethics Committee and the National Supervisory Authority of Welfare and Health. Helsinki University Hospital follows a standardised pancreatic resection procedure [6]. Staging of patients was determined according to the 7th edition of Pancreas cancer staging of American Joint Committee on Cancer (AJCC).

Patient characteristics are presented in Table 1 [Table 1 near here].

Median follow-up time was 2.1 years. Stage IV patients (n=2) were excluded from survival analyses. Three T0 patients (4%) were recorded in the neoadjuvant group. Prior to neoadjuvant therapy these patients had histologically confirmed PDAC. One of these patients had pathologically confirmed regional lymph node PDAC metastasis, resulting in two stage 0 complete responses. These two patients with stage 0 disease have lived for 4.8 and 4.2 years with no disease progression observed to date.

No difference in the administration of postoperative treatment was observed between patient groups. Out of the 48 (65%) patients treated with neoadjuvant therapy who were administered postoperative adjuvant therapy, 35 (73%) completed the given regimen. For those undergoing upfront surgery, 102 (68%) were administered adjuvant therapy and 66 (65%) were able to complete it. Survival analyses according to adjuvant therapy were calculated for all patients receiving adjuvant therapy, including those who were not administered the full adjuvant regimen. No significant differences in postoperative complications, including postoperative mortality, were recorded.

Neoadjuvant Therapy and Resectability

Neoadjuvant therapy was administered to borderline resectable patients only with the exception of one resectable patient taking part in a clinical trial. There were nine patients whose scans were not available to determine preoperative staging. Borderline resectable was defined as contact with the superior mesenteric vein or the portal vein with no distant metastases. Neoadjuvant therapy regimens consisted of folfirinox, single gemcitabine or combined with cisplatin, cabecitabin or nab-paclitaxel. Additional radiotherapy was administered to 29 (39%) patients. Radiotherapy alone was administered to one patient due to comorbidity. Tumour diameter in the axial plane was measured before and after neoadjuvant therapy on contrast-enhanced CT scans or, when unavailable, on MRI scans. The surgical tissue specimen were reviewed to confirm PDAC diagnosis.

Statistics

Fisher's exact test and linear-by-linear association were used for categorical variables. Mann-Whitney U-test was used for continuous variables and survival was estimated with the Kaplan-Meier method. Survival was compared with the Breslow test. Breslow denotes the early survival differences which in pancreatic cancer are more meaningful due to the dismal five-year survival rate. The main Kaplan-Meier analyses were, in addition, carried out with a landmark analysis; the landmark time was chosen as the median duration of neoadjuvant therapy. Multivariate analyses were carried out by using the Cox proportional hazards method. Tumour grade, stage, LNR, neoadjuvant therapy and adjuvant therapy were included in the multivariate model. The assumption of constant proportional hazard rate over time was tested by adding a time dependent

variable for each variable at a time. All variables met the assumption. Multivariate analyses were calculated with a time-dependent factor taking into account the time of surgery from the beginning of treatment to cover guarantee-time bias. Survival was calculated from the start of treatment, which was the first day of treatment for patients treated with neoadjuvant therapy and date of surgery for others, to death due to pancreatic cancer in DSS and disease progression first recorded in DFS. All statistical analyses were calculated with SPSS (v22, IBM, New York, NY, USA). A p-value <0.05 was considered significant and two-tailed tests were used.

Results

Between 2000 and 2015 (n=223) both median DSS and DFS were significantly longer in patients treated with neoadjuvant therapy than in patients undergoing upfront surgery [Table 2][Table 2 near here]. Patients treated in 2000-2009 (n=91) had no difference in DFS or DSS between compared groups, whereas, patients treated in 2010-2015 (n=132) showed a significant difference in both DSS and DFS between groups; patients treated with neoadjuvant therapy had both longer median DSS [Figure 1A] and DFS [Figure 1B] than patients undergoing upfront surgery [Table 2][Figures 1A and 1B near here].

Comparing patients treated with neoadjuvant therapy median DFS was longer in patients treated in 2010-2015 than in patients treated in 2000-2009, whereas, increase in DSS did not reach statistical difference. However, in patients undergoing

upfront surgery, no progress in DFS or DSS was observed between patients treated in 2000-2009 and 2010-2015[Supplement 1].

DSS and DFS were first evaluated according to tumour grade, stage and resection margins separately in patients treated with neoadjuvant therapy and those undergoing upfront surgery. DSS and DFS were additionally compared between patients treated with neoadjuvant therapy and patients undergoing upfront surgery according to these prognostic factors [Table 3][Table 3 near here]. A significant difference in favour of neoadjuvant therapy was noted in patients with poorly differentiated grade 3 tumour in both median DSS (30 vs. 11 months, $p=0.004$) [Figure 2A] and DFS (21 vs. 7 months, $p=0.001$) [Figure 2B][Figures 2A and 2B near here]. When dividing patients into groups according to stage and lymph node status, 0-IIA and IIB-III, there were no survival differences between groups. However, median DSS (34 vs. 20 months, $p=0.006$) [Figure 3A] and DFS (21 vs. 10 months, $p=0.001$)[Figure 3B] were recorded to be longer in patients with higher stage (IIB-III) treated with neoadjuvant therapy than upfront surgery [Figures 3A and 3B near here].

In the multivariate model including tumour grade, stage, LNR, neoadjuvant and adjuvant therapy, there were significant interactions between tumour grade and neoadjuvant therapy. Therefore, the model was split by tumour grade. After adjusting for other factors, neoadjuvant therapy presented with a protective effect on DSS and DFS in grade 3 patients (HR 0.37; 95% CI 0.17-0.84, $p=0.018$ and 0.40; 95% CI 0.17-0.92, $p=0.030$, respectively) [Supplement 2 and 3].

Grouping patients according to preoperative and postoperative treatment revealed that patients receiving perioperative treatment had both longest DSS and DFS

compared to those treated with neoadjuvant therapy and surgery and those treated with upfront surgery with or without adjuvant therapy. [Supplement 4].

Median time between the start of neoadjuvant therapy and surgery was 4 months (range 2-12 months, IQR 3-6 months). When comparing neoadjuvant regimens in 2000-2009 and 2010-2015, new agents such as folfinirox and nab-paclitaxel had been administered. Also, different agents were combined more often in the 2010s than in the 2000s [Supplement 6]. All adjuvant therapy regimens are listed in [Supplement 7].

Discussion

Whereas improvements in surgical techniques and perioperative care have decreased mortality and morbidity after surgery for pancreatic cancer, the overall survival of pancreatic cancer has not improved much during the past decades [1,18]. This study demonstrates that there has been some improvement in the survival of pancreatic cancer. Survival for borderline resectable patients treated with neoadjuvant therapy has improved during the past 15 years. These results offer hope for pancreatic cancer patients since neoadjuvant therapy gives patients with advanced disease a chance at resection and thus, the possibility of longer survival.

Over the studied time period, a comparison between patients treated with neoadjuvant therapy and those undergoing upfront surgery showed that both DSS and DFS were significantly longer in patients treated with neoadjuvant therapy. Interestingly, as there were no significant differences in patients treated in 2000-2009,

patients treated in 2010-2015 showed 9 months longer DSS and 12 months longer DFS in patients treated with neoadjuvant therapy. Improvement could be due to more effective systemic treatments. In the 2010s new regimens such as folfirinox and nab-paclitaxel have been used at our institution. In addition, our data showed that nowadays gemcitabine is more often combined with other agents, such as cisplatin. The improvement is emphasized by median DFS increasing significantly from the 2000s to 2010s, from 15 to 25 months. Although survival has not improved for patients undergoing upfront surgery, these results are encouraging for borderline resectable PDAC patients treated with neoadjuvant therapy. Similar findings have been reported before by Cloyd et al. [19], who divided 622 patients treated in 1990-2014 with neoadjuvant therapy and subsequent surgery into four successive time periods. Median overall survival improved drastically from 24 to 43 months. In addition, there was a randomized controlled trial in Korea aiming at 110 patients receiving neoadjuvant therapy. The aim was to compare survival to patients undergoing upfront surgery. However, the trial was ended at interim analysis, since the survival differences were so drastic in favour of neoadjuvant therapy [20].

Locally advanced unresectable pancreatic cancer has been treated with systemic chemotherapy with or without radiation for decades [21,22]. Overall survival has been reported to be 6-11 months [21,22]. Compared to our results, downstaging the disease to resectable with chemo(radio)therapy results in significantly longer survival (median 35 vs. 6-11 months). More aggressive surgery has been advocated as well, but it has been reported that extended pancreatectomy does not guarantee better survival for more advanced disease; mortality and morbidity after surgery increase but survival is not affected [23].

Tumour grade is a known prognostic factor in pancreatic cancer. It has even been postulated to have a stronger impact on survival than tumour size and lymph node positivity [24]. However, there are no studies on the prognostic impact of tumour grade in patients treated with neoadjuvant therapy. Our results suggest that neoadjuvant therapy may be effective especially in patients with poorly differentiated PDAC. This is supported by both longer DSS and DFS in patients with grade 3 tumour treated with neoadjuvant therapy than in patients undergoing upfront surgery; both median DSS and DFS showed a threefold increase in survival. The multivariate analyses also showed that neoadjuvant therapy had a protective effect on both DSS and DFS in patients with grade 3 tumours. Hence, it could be argued that oncologic treatment is more effective in aggressive disease. This is supported by the fact that similar survival differences were not recognised in patients with grade 1 or 2 tumours. However, tumour grade is not usually known prior to treatment due to scarce biopsy material. To achieve patient-specific treatment, more advanced diagnostic techniques are awaited.

Crippa et al. pondered the effectiveness of pancreatic surgery for grade 3 tumour patients [25]. Grade 3 tumour patients had clearly worse DSS (20 vs. 77 months) and DFS (9 vs. 63 months) when compared to grade 1 tumour patients. Also, the study showed that grade 3 tumour patients were most likely to benefit from adjuvant therapy (HR 2.11) [25]. The study recommended neoadjuvant therapy for grade 3 tumour patients. Our results support the recommendation.

Prognostic factors are universal for resectable pancreatic cancer patients and might not be adaptable to patients treated with neoadjuvant therapy. Table 4 shows that tumour grade, stage and resection margins are prognostic for patients undergoing

upfront surgery. However, they do not seem to apply to patients treated with neoadjuvant therapy in the same way.

Stage is widely recognised as a prognostic factor in pancreatic cancer. Lymph node negativity and especially low LNR have been associated with better survival in resectable pancreatic cancer [26]. Here, we divided patients into lymph node negative (0-IIA) and positive groups (IIB-III) according to stage. Here, too, neoadjuvant therapy seems to be effective in aggressive and advanced disease. Median DSS was 14 and DFS 11 months longer in stage IIB-III patients treated with neoadjuvant therapy than upfront surgery. There were no survival differences between lower stage patients.

There is most likely downstaging due to neoadjuvant therapy, which is supported by fewer nodal metastases, smaller tumour size and thus, lower stage. Patients treated with neoadjuvant therapy had a more favourable stage distribution than patients undergoing upfront surgery. This might, in fact, affect survival and multivariate analyses. De Geus et al. analysed neoadjuvant therapy and subsequent surgery versus upfront surgery and adjuvant therapy and found that neoadjuvant therapy showed a higher median survival in stage III patients (23 vs. 17 months) but not in early stage patients [13]. However, a larger study of 8026 patients comparing neoadjuvant therapy and upfront surgery found that neoadjuvant therapy has a significant survival benefit (26 vs. 21 months) over upfront surgery in early stage pancreatic cancer [12]. These results are inconclusive and demonstrate the inability to compare different studies due to heterogeneity and different criteria for study inclusion and resectability.

R1 resection is seen as a strong negative prognostic marker in pancreatic cancer and R1 resections are more commonly seen in borderline resectable pancreatic

cancer due to contact with nearby blood vessels [27]. In our study, the proportion of R0 and R1 resections did not differ between studied groups. Survival comparison according to R0/R1 status revealed no differences in DSS, however, DFS was longer in both R0 and R1 resected patients who had been treated with neoadjuvant therapy indicating that neoadjuvant therapy delays disease progression.

Grouping patients according to preoperative and postoperative treatment showed that clearly the longest survival was achieved with perioperative treatment and shortest with surgical treatment only. It is, however, unclear whether there is a meaningful difference in survival time between neoadjuvant therapy followed by surgery and surgery followed by postoperative adjuvant therapy. This, quite possibly, is dependent on tumour biology.

We acknowledge the limitations to this study; the study is retrospective, which could indicate selection bias. Also, the neoadjuvant therapy protocol has changed during the past 15 years with the addition of changing imaging and evaluation of resectability protocols. The multivariate results should be considered with caution due to limited number of patients with grade 3 tumours. However, these factors have been minimised by the fact that the propensity matched controls have been treated at the same time. The study does not consider a comparative non-resectable group, nor does it identify the patients with progressive disease during neoadjuvant therapy or those who could not finish their treatment due to other reasons. In Finland, preoperative diagnosis is mostly based on brush cytology, from which PDAC is impossible to diagnose.

In conclusion, this study emphasizes the fact that more aggressive disease and later stage PDAC patients benefit from neoadjuvant therapy; patients with grade 3

tumours presented with three times longer DSS and DFS when treated with neoadjuvant therapy. Survival has improved for borderline resectable PDAC patients treated with neoadjuvant therapy over the past 15 years. Whether to administer neoadjuvant therapy to early stage patients is still controversial. Due to possible selection bias and a vast variety of heterogeneous studies, further prospective and randomised controlled trials are much needed.

Acknowledgements and Disclosure Statement

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Figure legends:

Figure 1A. DSS in operated PDAC patients (2010-2015) according to preoperative treatment. Median survival for neoadjuvant therapy was 35 (95% CI 25-44) months and for upfront surgery 26 (95% CI 20-31) months, $p=0.008$.

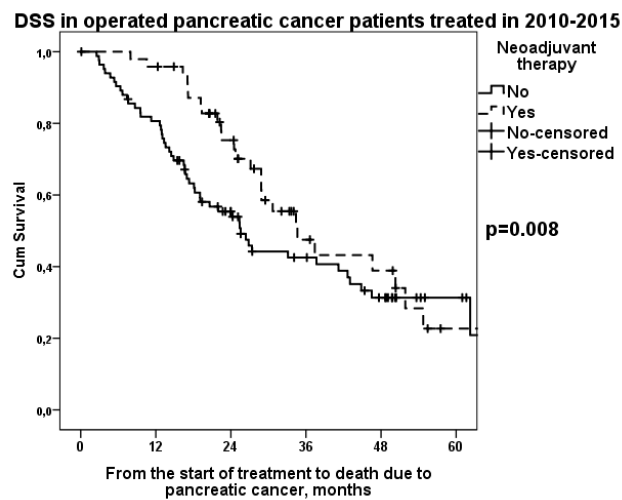


Figure 1B. DFS in operated PDAC patients (2010-2015) according to preoperative treatment. Median survival for neoadjuvant therapy was 25 (95% CI 13-36) months and for upfront surgery 13 (95% CI 6-21) months, $p=0.001$.

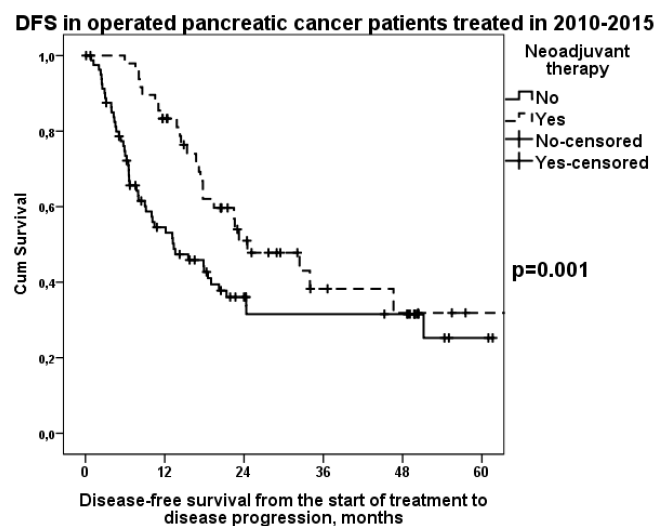


Figure 2A. DSS in patients with grade 3 tumour according to preoperative treatment. Patients: n(NEO)=14, n(US)=26. Median survival for neoadjuvant therapy 30 (95% CI 17-42) months and for upfront surgery 11 (95% CI 8-15) months, $p=0.004$. NEO=Neoadjuvant therapy, US=Upfront surgery.

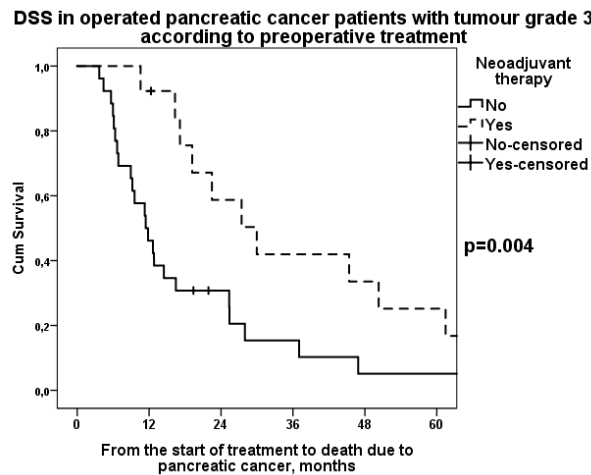


Figure 2B. DFS in patients with grade 3 tumour according to preoperative treatment. Patients: n(NEO)=14, n(US)=26. Median survival for neoadjuvant therapy was 21 (95% CI 11-31) months and for upfront surgery 7 (95% CI 5-8) months, $p=0.001$. NEO=Neoadjuvant therapy, US=Upfront surgery.

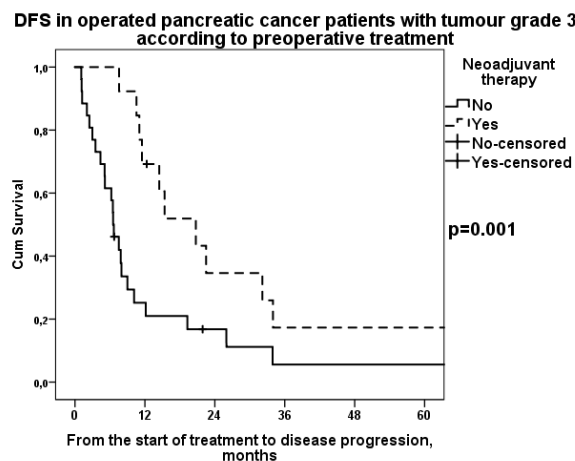


Figure 3A. DSS in operated stage IIB-III pancreatic cancer patients according to preoperative treatment. Patients: n(NEO)=35, n(US)=107. Median survival for neoadjuvant therapy was 34 (95% CI 29-40) months and for upfront surgery 20 (95% CI 14-26) months, $p=0.006$. NEO=Neoadjuvant therapy, US=Upfront surgery.

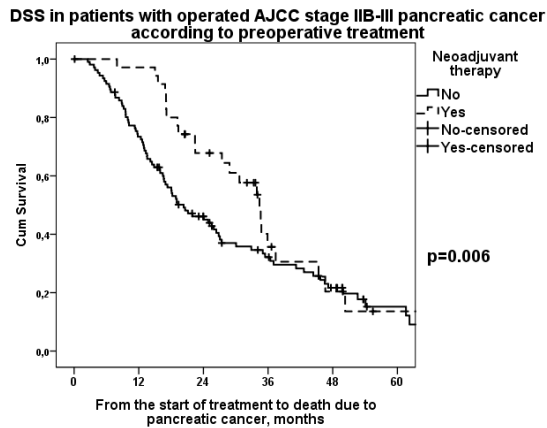


Figure 3B. DFS in operated stage IIB-III pancreatic cancer patients according to preoperative treatment. Patients: n(NEO)=35, n(US)=107. Median survival for neoadjuvant therapy was 21 (95% CI 12-29) months and for upfront surgery 10 (95% CI 7-13) months, $p=0.001$. NEO=Neoadjuvant therapy, US=Upfront surgery.

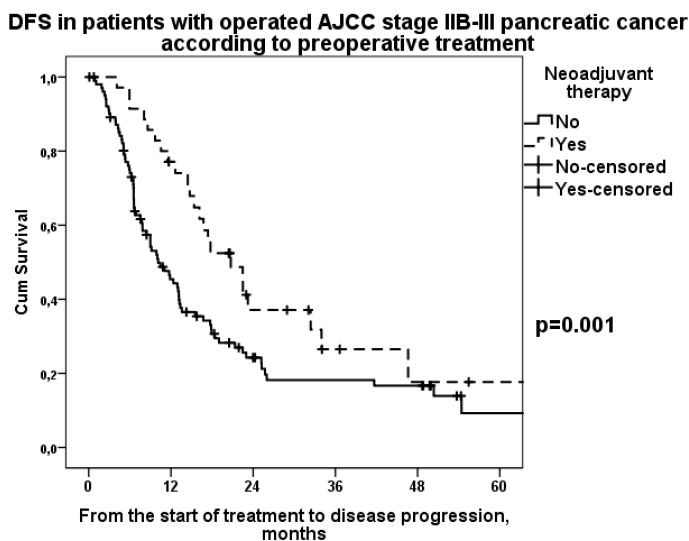


Table 1. Patient characteristics of PDAC patients operated in 2000-2015 according to preoperative treatment.

	NEO (n=75)	US (n=150)	p-value
Age at operation, median (range)	65 (40-83)	66 (45-82)	NS
≥65 years	39 (50%)	79 (53%)	NS
Gender, female	42 (56%)	83 (55%)	NS
pTN* (AJCC 7 th edition)			
T0	3 (4%)	0	0.001
T1	9 (12%)	5 (3%)	
T2	18 (25%)	30 (20%)	
T3	42 (58%)	115 (77%)	
T4	1 (1%)	0	
N0	38 (51%)	42 (28%)	0.001
N1	36 (49%)	108 (72%)	
LNR*			
<20 %	66 (89%)	109 (74%)	0.009
≥20 %	8 (11%)	39 (26%)	
Stage* (AJCC 7 th edition)			
0	2 (3%)	0	0.000
IA	5 (7%)	3 (2%)	
IB	10 (14%)	16 (11%)	
IIA	20 (27%)	23 (15%)	
IIB	34 (47%)	107 (71%)	
III	1 (1%)	0	

IV**	1 (1%)	1 (1%)	
pTumor size (mm), median (IQR)	25 (20-30)	30 (25-40)	0.000
Grade*			
1	11 (15%)	27 (18%)	NS
2	48 (66%)	97 (65%)	
3	14 (19%)	26 (17%)	
R0 resection*	58 (82%)	106 (75%)	NS
Vascular resection	34 (45%)	49 (33%)	NS
Perineural invasion*	47 (63%)	120 (81%)	0.005
Perivascular invasion*	16 (21%)	58 (39%)	0.010
Imaging (median in mm, range)			
Tumour size pre-therapy	31 (10-89)		
Tumour size post-therapy	23 (0-47)		
Size difference	9 (0-42)		
Missing/inadequate imaging	9 (12%)		
Preoperative laboratory results***			
CA 19-9 (ln(kU/l)), median (IQR)	4.4 (2.6-5.9)	4.8 (3.4-6.5)	NS
CEA (µg/l), median (IQR)	2.7 (1.7-3.9)	2.9 (1.8-5.0)	NS

NEO=Neoadjuvant therapy, US=Upfront surgery, AJCC=American Joint Committee on Cancer, LNR=lymph node ratio, IQR=interquartile range, NS=non-significant.

*Missing data: two patients lacked adequate TNM classification and stage, three patients' lymph node metastases were inconclusive. Information on perineural and perivascular invasion was missing in one patient. Resection margin status was missing in seven patients. No grade available in two patients due to complete response.

**Preoperatively treated patient had an adrenal metastasis, and patient undergoing upfront surgery had a para-aortal lymph node metastasis. Metastases were not confirmed before surgery. These patients were excluded from survival analyses.

***Mann-Whitney U-test. Natural logarithm was taken from CA19-9 value.

All 2x2 tests were done by using the Fisher's exact test. Linear by linear association was used for tables with more than two rows. Missing data were excluded.

Table 2. DSS and DFS in operated PDAC patients according to preoperative treatment.

	NEO (95% CI) months	US (95% CI) months	p-value
Patients treated in 2000-2015 (n=223)			
DSS	34 (29-39)	26 (20-32)	0.016
DFS	22 (17-27)	13 (9-17)	0.001
Patients treated in 2000-2009 (n=91)			
DSS	30 (22-38)	27 (17-37)	NS
DFS	15 (10-19)	12 (10-15)	NS
Patients treated in 2010-2015 (n=132)			
DSS	35 (25-44)	26 (20-31)	0.008
DFS	25 (13-36)	13 (6-21)	0.001

NEO=neoadjuvant therapy, US=upfront surgery, DSS=disease-specific survival, DFS=disease-free survival, NS=non-significant. Survival was estimated with Kaplan-Meier and compared with the Breslow test.

Table 3. DSS and DFS survival in operated PDAC patients according to different prognostic parameters and preoperative treatment.

	NEO (95% CI) months	p-value	NEO vs. US p-value	US (95% CI) months	p-value
DSS					
Tumour grade 1	36 (34-38)	NS	NS	43 (32-54)	0.000

Tumour grade 2	31 (27-34)		NS	27 (20-35)	
Tumour grade 3	30 (17-42)		0.004	11 (8-15)	
DFS					
Tumour grade 1	23 (15-31)	NS	NS	18 (12-25)	0.000
Tumour grade 2	18 (12-25)		NS	13 (8-18)	
Tumour grade 3	21 (11-31)		0.001	7 (5-8)	
DSS					
Stage 0-IIA	31 (25-37)	NS	NS	45 (33-56)	0.004
Stage IIB-III	34 (29-40)		0.006	20 (14-26)	
DFS					
Stage 0-IIA	19 (13-26)	NS	NS	24 (7-41)	0.003
Stage IIB-III	21 (12-29)		0.001	10 (7-13)	
DSS					
R0 margin	36 (34-38)	NS	NS	29 (21-37)	NS
R1 margin	31 (14-47)		NS	17 (12-21)	
DFS					
R0 margin	23 (17-29)	NS	0.028	16 (11-21)	0.001
R1 margin	17 (11-22)		0.024	7 (2-11)	

NEO=neoadjuvant therapy, US=upfront surgery, DSS=disease-specific survival, DFS=disease-free survival, NS=non-significant. Survival times were estimated with Kaplan-Meier and compared with the Breslow test. Stage according to AJCC 7th edition guidelines.